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JC14 Rec'd PCT/PTO 16 JAN 2002

Form PTO-1390U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (REV 10-95) TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	ATTORNEY'S DOCKET NUMBER **0702-020040** U.S. APPLICATION NO. (If known, see 37 CFR 1.5) **10/031509**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATES CLAIMED
PCT/EP00/06917	**17.07.00 (17 July 2000)**	**16.07.99 (16 July 1999)**

TITLE OF INVENTION **INHIBITION OF RENAL UPTAKE OF MOLECULES THAT ARE POTENTIALLY DAMAGING FOR THE KIDNEY**

APPLICANT(S) FOR DO/EO/US **Eric P. KRENNING, Marion DE JONG; Roelf VALKEMA**

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items And other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
    a. WO 01/05383-Front Page, Specification, Claims And Drawings (25 pp.)
    b. International Search Report (5 pp.)

U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 10/031509	INTERNATIONAL APPLICATION NO. PCT/EP00/06917	ATTORNEY'S DOCKET NUMBER 0702-020040

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):

Search Report has been prepared by the EPO or JPO..... **$890.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) **$710.00**

No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))..... **$740.00**

Neither international preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO..... **$1040.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... **$100.00**

CALCULATIONS PTO USE ONLY

ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	32 - 20	12	X **$18.00**	$ 216.00	
Independent claims	2 - 3 =	0	X **$84.00**	$ 0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$280.00**	$ 0.00	
TOTAL OF ABOVE CALCULATIONS =				$ 1236.00	
Reduction of 1/2 for filing by small entity, if applicable.				$ 0.00	
SUBTOTAL =				$ 1236.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0.00	
TOTAL NATIONAL FEE =				$ 1236.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 0.00	
TOTAL FEES ENCLOSED =				$ 1236.00	
				Amount to be: Refunded	$
				Charged	$

a. ☒ A check in the amount of $ **1236** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. ____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Assistant Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-0650. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
Barbara E. Johnson
700 Koppers Building
436 Seventh Avenue
Pittsburgh, Pennsylvania 15219-1818
Telephone: (412) 471-8815
Facsimile: (412) 471-4094

SIGNATURE

Barbara E. Johnson
NAME

31,198
REGISTRATION NUMBER

PATENT APPLICATION/PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: ATTORNEY'S DOCKET NUMBER

Eric P. KRENNING
Marion DE JONG
Roelf VALKEMA

0702-020040

PCT/EP00/06917

ENTITLED
INHIBITION OF RENAL UPTAKE OF MOLECULES THAT ARE POTENTIALLY DAMAGING FOR THE KIDNEY

To **BOX PCT**
Attention: DO/EO/US

Assistant Commissioner for Patents
Washington, D.C. 20231

EXPRESS MAIL CERTIFICATE

"Express Mail" Label Number **EL873414169US**

Date of Deposit January 16, 2002

I hereby certify that the following attached paper or fee

Transmittal Letter To The United States Designated/Elected Office (DO/EO/US) Concerning A Filing Under 35 U.S.C. 371 (original and two (2) copies) And Check In The Amount Of $1236.00 For Filing Fee; Letter Recognizing Attorneys (2 pp.); Preliminary Amendment; WO 01/05383 Front Page With Abstract, Specification, Claims And Drawings (25 pp.); International Search Report (5 pp.)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

K.T. Berthold
(Typed name of person mailing paper or fee)

K.T. Berthold
(Signature of person mailing paper or fee)

PATENT APPLICATION/PCT
Attorney Docket No. 702-020040

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Eric P. KRENNING Marion DE JONG Roelf VALKEMA	: : :	INHIBITION OF RENAL UPTAKE OF MOLECULES THAT ARE POTENTIALLY DAMAGING FOR THE KIDNEY
International Application No. PCT/EP00/06917	: :	
International Filing Date 17 July 2000	: :	
Priority Date Claimed 16 July 1999	: :	
Serial No. Not Yet Assigned	:	
Filed Concurrently Herewith	:	

Pittsburgh, Pennsylvania
January 16, 2002

PRELIMINARY AMENDMENT

Box PCT
Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-identified patent application as follows:

IN THE SPECIFICATION:

On page 1, after the title, please insert the following section headings:

BACKGROUND OF THE INVENTION

1. Field of the Invention

Before the paragraph beginning at page 1, line 7, please insert the following section heading:

2. Description of the Related Art

Before the paragraph beginning at page 4, line 8, please insert the following section heading:

SUMMARY OF THE INVENTION

Please replace the partial paragraph beginning at page 4, line 8 with the following rewritten paragraph:

The present invention is a combination of:

Before the paragraph beginning at page 4, line 25, please insert the following section headings and specification paragraphs:

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the ratio between [^{111}In-DTPA-D-Phe^{1}]octreotide uptake in various organs in the presence or absence of 1 L lysine/arginine infusion (25/25 g; administered over 4 hours);

Figure 2 shows the ration between [^{177}Lu-DOTA, Tyr^{3}]octreotate uptake in various organs in the presence or absence of 1 L lysine/arginine infusion (25/25 g; administered over 4 hours);

Figure 3 shows the ratio between [^{111}In-DTPA-D-Phe^{1}]octreotide uptake in various organs in the presence or absence of 1 L glucose/saline solution, administered over 4 hours; and

Figure 4 shows between [^{111}In-DTPA-D-Phe^{1}]octreotide uptake in the left kidney after a 0.5 + 3.5 hour infusion of various amino acid compositions.

DETAILED DESCRIPTION OF THE PREFERED EMBODIMENTS

With reference to Figures 1-4, it was found that 50% inhibition in renal uptake of [^{111}-In-DTPA-D-Phe^{1}]octreotide in rats could be achieved by D-Lysine or L-lysine at 400 mg/kg. L-arginine alone gave a reduction of 20-30% at an equimolar dose. In human studies 15, 21 and 40% reduction of kidney uptake of [^{111}In-DTPA-D-Phe^{1}]octreotide was reached using a dose of 25, 50 and 75 g L-lysine, respectively. The doses of 25 and 50 g L-lysine were well tolerated without any toxicity noted, but the 75 g L-lysine dose was associated with severe hyperkalemia in 50% of the patients. Hyperkalemia may result in acute and life-threatening cardiotoxicity.

Please delete the specification paragraph beginning at page 4, line 25.

IN THE CLAIMS:

Please cancel original claims 1-20 and rewrite them as new claims 21-52 as follows:

21. A method for the preparation of a composition for inhibiting renal uptake of substances, in particular proteins or peptides, that may be damaging to the kidneys and that are used for therapeutical or diagnostic purposes, the method comprising:

providing the combination of a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof; and

a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

22. The method as claimed in claim 21, wherein the positively charged second molecule is a positively charged amino acid, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

23. The method as claimed in claim 22, wherein the positively charged amino acid is selected from the group consisting of arginine, ornithine and citrulline, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

24. The method as claimed in claim 21, wherein the first compound is lysine selected from D-lysine, L-lysine or poly-lysine.

25. The method as claimed in claim 21, wherein the first compound is lysine and the second compound is arginine.

26. The method as claimed in claim 21, wherein the amount of the first compound is 10-45 grams per treatment.

27. The method as claimed in claim 21, wherein the amount of the first compound is 15-35 grams per treatment.

28. The method as claimed in claim 21, wherein the amount of the first compound is 20-30 grams per treatment.

29. The method as claimed in claim 21, wherein the amount of the first compound is about 25 grams per treatment.

30. The method as claimed in claim 21, wherein the amount of the second compound is 15-45 grams per treatment.

31. The method as claimed in claim 21, wherein the amount of the second compound is 15-35 grams per treatment.

32. The method as claimed in claim 21, wherein the amount of the second compound is 20-30 grams per treatment.

33. The method as claimed in claim 21, wherein the amount of the second compound is about 25 grams per treatment.

34. The method as claimed in claim 21, wherein the first compound is lysine in an amount of about 25 grams and the second compound is arginine in an amount of about 25 grams per treatment.

35. The method as claimed in claim 21, wherein the two compounds are administered in about 1 L infusion fluid over a period of about 4 hours.

36. The method as claimed in claim 21, wherein the substances that may be damaging to the kidneys, and of which the renal tubular uptake is to be inhibited are proteins, peptides or monoclonal antibodies, in particular proteins, peptides or monoclonal antibodies that are inherently toxic, that are coupled to a radionuclide, a cytostatic agent, a toxic agent, a metal, or a combination thereof, or cytostatic agents and nephrotoxic antibiotics per se.

37. A therapeutical composition for the inhibition of the renal uptake of substances, in particular proteins or peptides, that may be damaging to the kidneys and that are used for therapeutical or diagnostic purposes, which composition comprises one or more pharmaceutically acceptable excipients, carriers or diluents and a combination of:

a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof; and

a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

38. The therapeutical composition as claimed in claim 37, wherein the positively charged second molecule is a positively charged amino acid, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

39. The therapeutical composition as claimed in claim 38, wherein the positively charged amino acid is selected from the group consisting of arginine, ornithine and citrulline, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

40. The therapeutical composition as claimed in claim 37, wherein the first compound is lysine selected from D-lysine, L-lysine or poly-lysine.

41. The therapeutical composition as claimed in claim 37, wherein the first compound is lysine and the second compound is arginine.

42. The therapeutical composition as claimed in claim 37, wherein the amount of the first compound is 10-45 grams per treatment.

43. The therapeutical composition as claimed in claim 37, wherein the amount of the first compound is 15-35 grams per treatment.

44. The therapeutical composition as claimed in claim 37, wherein the amount of the first compound is 20-30 grams per treatment.

45. The therapeutical composition as claimed in claim 37, wherein the amount of the first compound is about 25 grams per treatment.

46. The therapeutical composition as claimed in claim 37, wherein the amount of the second compound is 15-45 grams per treatment.

47. The therapeutical composition as claimed in claim 37, wherein the amount of the second compound is 15-35 grams per treatment.

48 The therapeutical composition as claimed in claim 37, wherein the amount of the second compound is 20-30 grams per treatment.

49. The therapeutical composition as claimed in claim 37, wherein the amount of the second compound is about 25 grams per treatment.

50. The therapeutical composition as claimed in claim 37, wherein the first compound is lysine in an amount of about 25 grams and the second compound is arginine in an amount of about 25 grams per treatment.

51. The therapeutical composition as claimed in claim 37, wherein the two compounds are present in about 1 L infusion fluid.

52. The method for inhibiting the renal uptake of proteins or peptides, that are used for therapeutical or diagnostic purposes, in a subject, which method consists of the administration of a therapeutical composition as claimed in claim 37.

IN THE ABSTRACT:

After the claims, please insert a page containing the Abstract Of The Disclosure, which is attached hereto as a separately typed page.

REMARKS

The specification and claim amendments have been made in order to conform this patent application to customary United States patent practice.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attachment is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE".

Examination and allowance of pending claims 21-52 are respectfully requested.

Respectfully submitted,

WEBB ZIESENHEIM LOGSDON
ORKIN & HANSON, P.C.

By _____

Barbara E. Johnson
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INHIBITION OF RENAL UPTAKE OF MOLECULES THAT ARE POTENTIALLY DAMAGING FOR THE KIDNEY

ABSTRACT OF THE INVENTION

The invention relates to the use of the combination of a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof, and a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof, for the preparation of a composition for inhibiting renal uptake of substances, in particular proteins or peptides, that may be damaging to the kidneys, and that are used for therapeutical or diagnostic purposes. The combination consists advantageously of lysine and arginine.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Partial paragraph beginning at page 4, line 8 has been amended as follows:

[This is achieved by the invention by the use of the] The present invention is a combination of:

PATENT APPLICATION/PCT
Attorney Docket No. 702-020040

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Eric P. KRENNING Marion DE JONG Roelf VALKEMA	: : :	INHIBITION OF RENAL UPTAKE OF MOLECULES THAT ARE POTENTIALLY DAMAGING FOR THE KIDNEY
International Application No. PCT/EP00/06917	: :	
International Filing Date 17 July 2000	: :	
Priority Date Claimed 16 July 1999	: :	
Serial No. Not Yet Assigned	:	
Filed Concurrently Herewith	:	

Pittsburgh, Pennsylvania
January 16, 2002

LETTER RECOGNIZING ATTORNEYS

Box PCT
Assistant Commissioner for Patents
Washington DC 20231

Sir:

Enclosed are appropriate papers for initiating the national phase of the above-identified PCT application, comprising a specification, claims, abstract and drawings. A Preliminary Amendment is also enclosed.

Please accept the application for purposes of granting a filing date and recognize Barbara E. Johnson, Richard L. Byrne and Darrell E. Williams, Registration Nos. 31,198, 28,498 and 45,222, respectively, as attorneys in this application, pending the filing of a formal Declaration and Power of Attorney.

Kindly direct all communications relating to this application to **Barbara E. Johnson**.

(1)

Respectfully submitted,

WEBB ZIESENHEIM LOGSDON
ORKIN & HANSON, P.C.

By _____
Barbara E. Johnson, Reg. No. 31,198
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INHIBITION OF RENAL UPTAKE OF MOLECULES THAT ARE POTENTIALLY DAMAGING FOR THE KIDNEY

The present invention relates to the inhibition of renal uptake of molecules that are potentially damaging for the kidney.

Radionuclide labeled peptides and also monoclonal antibodies or their fragments and other compounds like certain antibiotics undergo undesired renal uptake and cellular retention leading to a high kidney dose, or concentration. In the case of diagnosis or therapy with radiolabeled proteinaceous compounds, like peptides and monoclonal fragments, the uptake of these compounds by the kidneys leads to a reduction in the detection sensitivity of perirenal tumors or an increase in kidney radiotoxicity.

In certain other situations a general overload of proteins in the kidney can occur, such as in the case of amino acid metabolism diseases, induced catabolism or prolonged physical exercise, e.g. long-distance running.

Increased amounts of protein or raised doses of radiation or toxic substances in the kidneys may eventually lead to kidney damage.

International patent application No. WO91/04755, filed September 24, 1990, teaches methods to reduce non-target kidney retention of immunoconjugates, metabolites thereof, including other substances, such as peptides, by coadministration of a non-target moiety, such as lysine, or other amino acids having a free amino group. The application discloses only experimental results with mice showing that higher doses of lysine as a non-target reduction moiety improved results, i.e. the percentage of the injected immunoconjugate dose detected in the kidney is decreased. However, no information is provided concerning the possible toxicity of the method, and no data in humans were supplied. It is a known fact that there are differences in the physiology, including the renal physiology between mice and humans.

Additionally, it is known that infusion of amino acid solutions can induce side effects, including hyperkalemia (e.g. Ponce SP, et al. Medicine 64: 357-370, 1985, and Sartori S, et al. Recenti Progressi in Medicina 82(6): 275-277, 1991). This has been reported in particular for arginine (e.g. Massara F, et al. Diabete et Metabolisme 5(4):297-300, 1979), but it is also known in general medical practice for lysine, among others (Speck SP. in: Rakel RE, ed. Saunders Manual of Medical Practice; W.B. Saunders Company, Philadelphia, 2000, pp 885-888).

It is furthermore a known practice to use in patients an infusion of commercially available cocktails of various amino acids to lower the uptake of radiolabeled pharmaceuticals such as [^{111}In-DTPA-D-Phe^{1}]octreotide in the kidney (Hammond et al. in Br. J. Cancer 67, 1437-1439 (1993), Barone R, et al., J. Nucl. Med, 41: 94P (2000)). Such cocktails usually comprise a total amount of about 100 grams or more of various amino acids. In order to keep the osmolarity of such mixed amino acid solutions tolerable for human infusion, the total volume will be in the range of 2 liters.

This type of treatment has the observed disadvantageous side-effect that patients may suffer from severe vomiting, presumably caused by toxicity of the high total amount of amino acids administered. Additionally, the infusion of any volume of 2 liters within 4 hours, especially when it is hyperosmolar, can be dangerous to patients with impaired cardiac or renal function.

For the purpose of the invention, i.e. inhibiting renal uptake, it is necessary to reach a particular serum level of amino acids within a relatively short time, because excretion of the bulk of radiopharmaceuticals occurs within the first 4 to 6 hours after administration. During this time the radiopharmaceuticals may be taken up by the kidneys. It is thus not possible to avoid the side-effect of vomiting

by administering the amino acid cocktail over a longer period of time.

Furthermore, it has been described by De Jong et al. in J. Nucl. Med 37(8): 1388-1392 (1996) that uptake in the rat kidneys of the [^{111}In-DTPA-D-Phe^1]octreotide can be inhibited by 50% by intravenous administration of the amino acid L-lysine alone (400 mg/kg). In a further article by Bernard et al. in J. Nucl. Med. 38: 1929-1933 (1997) it was demonstrated that also D-lysine is capable of reducing the rat renal uptake of [^{111}In-DTPA-D-Phe^1]octreotide and ^{90}Y-DOTA,Tyr^3-octreotide.

However, treatment with lysine has also various disadvantages. It was for example found in humans that L-lysine in an effective total dose of 75 g (see examples for details) may lead to severe hyperkalemia which may result in acute and life-threatening cardiotoxicity in 50% of the patients.

In WO96/29087 it is also suggested to reduce kidney uptake of antibody fragment conjugates by administration of lysine or poly-lysine. It is taught in said application that toxicity of lysine can be avoided by using D-lysine because it does not occur naturally in humans or animals and is believed to be metabolically inert, thereby reducing the risk of toxic side-effects associated with the use of L-lysine. The prescribed dosage of monomeric lysine in this application is 1-200 g. The examples do not give results of treatments with humans with lysine alone. The only experiments in humans are performed with the commercially available amino acid solution Periamin X^{TM}. According to the invention it is now shown that even 75 g of lysine is too high a dose. This already indicates that WO96/29087 may mention, but does not really enable the use of lysine in humans.

From the prior art it thus follows that reduction of renal uptake of unwanted proteinaceous materials can be achieved by either the use of amino acid cocktails that are commonly used as parenteral food

supplements or with lysine alone. Either method has however the disadvantage that it may lead to toxic effects in humans.

It is therefore the object of the invention to provide a new improved way of inhibiting the renal tubular uptake of various types of proteinaceous molecules, such as proteins, peptides and antibodies.

This is achieved by the invention by the use of the combination of:

- a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof, and
- a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof,

for the preparation of a composition for inhibiting renal uptake of proteins or peptides, that are used for therapeutical or diagnostic purposes.

Preferred positively charged compounds are amino acids, e.g. arginine, ornithine or citrulline. The preferred positively charged amino acid for use together with lysine is arginine.

It was found that 50% inhibition in renal uptake of [^{111}In-DTPA-D-Phe^{1}]octreotide in rats could be achieved by D-Lysine or L-lysine at 400 mg/kg. L-arginine alone gave a reduction of 20-30% at an equimolar dose. In human studies 15, 21 and 40% reduction of kidney uptake of [^{111}In-DTPA-D-Phe^{1}]octreotide was reached using a dose of 25, 50 and 75 g L-lysine, respectively. The doses of 25 and 50 g L-lysine were well tolerated without any toxicity noted, but the 75 g L-lysine dose was associated with severe hyperkalemia in 50% of the patients. Hyperkalemia may result in acute and life-threatening cardiotoxicity.

The combination of L-lysine and L-arginine, however, shows a synergistic effect and is more effective

than both compounds alone at equimolar concentrations in reducing renal uptake of radiolabeled peptides. Using the combination, lower doses of the two amino acids can therefore effectively inhibit the (radio)pharmaceutical renal uptake and simultaneously prevent hyperkalemia and cardiotoxicity. The normal serum potassium values lie between 3.5 and 5.3 mmol/L. Values between 5.3 and 6.0 mmol/L are a grey area. Values above 6.0 mmol/L are not acceptable, and cardiotoxicity may occur.

An additional advantage of the use of the two compounds of the invention is that the total infusion volume can be kept to 1 liter, which is safer than 2 liter in patients with compromised renal or cardiac function.

The treatment of the invention was found to have a lower impact on the increase in potassium level in serum than a treatment with 75 g lysine in 1500 mL. Whereas in the latter case 3 out of 6 patients had a maximum potassium level above the critical value of 6.0 mmol/L, the treatment of the invention resulted in only one out of eleven patients having a maximum potassium value of 6.0 mmol/L.

It is assumed that a possible mechanism of action of the invention is based on a blockade of megalin, a type I membrane glycoprotein of 4630 amino acids, 600 kDa, and having a pI of 4.6 that mediates renal tubular reabsorption. Megalin's mechanism of action is based on endocytosis through coated pit vesicles. Megalin transports positively charged molecules and is found on the brush border of proximal tubular cells, thyroid follicular cells, parathyroid cells, in the mammary gland, placenta, yolk sac and on lung type II pneumocytes.

The inhibition of renal uptake of proteins and peptides can be effected during therapy and diagnosis to protect the kidneys from detrimental side-effects of the therapeutic or diagnostic materials. In addition, when tissues surrounding the kidneys are subjected to

localization with radiolabeled proteins or peptides, renal uptake of these radioactive materials may interfere with the scintigraphic visualization due to radiation from the kidneys that obscures the radiation from these surrounding tissues. Inhibition of accumulation of radioactivity in the kidneys is then also desirable.

It was also found according to the invention that after treatment with the combination of L-lysine plus L-arginine during radiotherapy with [^{177}Lu-DOTA,Tyr^3] octreotate none of the 11 patients treated suffered from vomiting. In contrast, with the treatment with a cocktail of several amino acids (see examples for the details) 42% of the patients vomited who received radiotherapy with ^{90}Y-DOTA,Tyr^3-octreotide. In 45% of these patients vomiting was very severe, i.e. 5 to 30 times. In another experiment it was found that in only 8% of treatments with the L-lysine and L-arginine combination vomiting occurred, mainly observed in one single patient, and this were probably not related to this combination.

The invention is suitable for inhibiting the renal uptake of all sorts of proteinaceous materials, such as proteins, peptides and monoclonal antibodies or their fragments. Renal uptake is to be avoided in case the proteinaceous materials are inherently toxic for the kidneys, and when they are coupled to a toxin, a radionuclide, a cytostatic agent or other potentially detrimental product. Renal uptake of nephrotoxic antibiotics or cytostatic agents per se is also to be prevented. In some cases the uptake by the kidneys of other, non-detrimental proteins can also be a problem. Protein is metabolized by the liver and excreted by the kidneys into the urine. A high protein load causes damage to these organs. In addition, diseases related to amino acid metabolism could lead to a protein overload in the kidneys.

Specific examples of diagnosis and therapies in which the composition of the invention could be used to inhibit or prevent renal uptake of the diagnostic or

therapeutic agent are the use of radiolabelled peptides, including but not limited to octreotide and other somatostatin analogs, labelled with ^{111}In, ^{90}Y, ^{177}Lu, ^{131}I or any other suitable radionuclide. Further examples are the diagnostic and therapeutic application of monoclonal antibodies or their fragments, nephrotoxic drugs such as antibiotics and cytostatic drugs.

In all these and other situations, the inhibition of the uptake of proteins or pharmaceuticals by the kidneys according to the invention can be beneficial.

The invention further relates to therapeutical compositions for inhibiting the renal uptake of proteins or peptides, that are used for therapeutical or diagnostic purposes, which composition comprises one or more suitable excipients, carriers or diluents and a combination of

- a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof, and
- a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

Preferred positively charged compounds are amino acids, e.g. arginine, ornithine or citrulline. The preferred positively charged amino acid for use together with lysine is arginine.

In a preferred embodiment of the composition it comprises lysine and arginine. The amount of lysine in the composition is between 10 and 45 grams, preferably between 15 and 35 grams, more preferably between 20 and 30 grams, most preferably about 25 grams. The amount of arginine is between 15 and 45 grams, preferably between 15 and 35 grams, more preferably between 20 and 30 grams, most preferably about 25 grams. Such amounts are preferred for administration in 1 L over 4 hours.

Preferably the total amount of the two compounds does not exceed 100 grams, is preferably less than 75 grams and is more preferably not more than 50 grams. The amounts given are intended for adults. For children the usual modifications can be made.

In this application the term "first compound" should be understood to refer to one or more members selected from the group consisting of lysine, poly-lysine, pharmaceutically acceptable salts or carboxyl derivatives thereof, as well as amino acids or other proteinaceous moieties having a free amino group with a pKa substantially similar or equal to that of lysine. The "second compound" is to be understood to refer to one or more positively charged compounds, preferably selected from among positively charged amino acids, more preferably selected from among arginine, ornithine and citrulline or poly-amino acids or pharmaceutically acceptable salts or carboxyl derivatives of the positively charged amino acids. The preferred combination is such that the first compound is lysine, which may be either D-lysine, L-lysine or poly-lysine. The second compound is preferably arginine, which may be either D-arginine, L-arginine or poly-arginine.

The therapeutical composition of the present invention can be in an oral or parenteral dosage form. Parenteral dosage forms include intravenous, intraarterial, intraperitoneal, intramuscular and subcutaneous dosage forms, preferably intravenous dosage forms. Administration may be via a single or via multiple boluses, or by continuous or discontinuous infusion and is preferably by continuous infusion over 4 hours, starting about 30 minutes prior to administration of the radiopharmaceutical.

The combination of compounds of the present invention may be administered in any pharmaceutically acceptable solution. A solution is said to be pharmaceutically acceptable if its administration can be tolerated by a recipient patient. Sterile phosphate-

buffered saline is one example of a pharmaceutically acceptable carrier, as is Ringer lactate, Hartman's solution or a mixture of glucose and saline. Other suitable carriers are well-known to those skilled in the art.

The present invention will be further illustrated in the examples that follow and that are not intended to limit the scope of the invention.

In the examples reference is made to the following figures:

Figure 1 shows the ratio between [^{111}In-DTPA-D-Phe^1]octreotide uptake in various organs in the presence or absence of 1 L lysine/arginine infusion (25/25 g; administered over 4 hours). Filled dots represent non-targeted accumulation of the radiopharmaceutical. Open squares represent the targeted accumulation of the radiopharmaceutical.

Figure 2 shows the ratio between [^{177}Lu-DOTA, Tyr^3]octreotate uptake in various organs in the presence or absence of 1 L lysine/arginine infusion (25/25 g; administered over 4 hours). Filled dots represent non-targeted accumulation of the radiopharmaceutical. Open squares represent the targeted accumulation of the radiopharmaceutical.

Figure 3 shows the ratio between [^{111}In-DTPA-D-Phe^1]octreotide uptake in various organs in the presence or absence of 1 L glucose/saline solution, administered over 4 hours. Filled dots represent non-targeted accumulation of the radiopharmaceutical. Open squares represent the targeted accumulation of the radiopharmaceutical.

Figure 4 shows between [^{111}In-DTPA-D-Phe^1]octreotide uptake in the left kidney after a 0.5 + 3.5 hour infusion of various amino acid compositions.

EXAMPLES

MATERIALS

Composition of infusion fluids

A. Lys/Arg

Combination of L-lysine and L-arginine (total 1000 mL)

- L-arginine HCl 10% 250 mL (=25 grams of L-arginine)
- L-lysine HCl 5% 500 mL (=25 grams of L-lysine)
- HCl 25% is added to achieve pH 7.4
- NaCl 0.9% is added to achieve a total volume of 1000 mL

The osmolarity of this combination is ca. 400 mosmol/L
The total quantity of amino acids is 50 grams.

B. Cocktail of various amino acids (total 2030 mL)

- Aminosteril N-Hepa 8% 1500 mL
- Ringer lactate 500 mL
- Magnesium sulfate (7-water) 10% 30 mL

The osmolarity of this combination is ca. 700 mosmol/L
The total quantity of amino acids is 124.5 grams.

Aminosteril N-Hepa 8% is a commercially available solution containing a mixture of amino acids (Fresenius AG, Gluckensteinweg 5, D-6380 Bad Homburg v.d. H., Germany). The composition is given herein below.
Ringer lactate is a mineral solution containing NaCl 0.6%, $CaCl_2.2H_2O$ 0.04%, Na-lactate 0.322% (Baxter B.V., Energielaan 3, NL-5405 AD Uden, The Netherlands)

Composition of Aminosteril N Hepa 8% infusion fluid

SUBSTANCE	QUANTITY (g/L)		Total in 1500 mL	
L-isoleucine	10,40		15,600	
L-leucine	13,09		19,635	
L-lysinemonoacetate (= 6,88 g L-lysine)	9,71	(6.88)	14,565	(10.32)
L-methionine	1,10		1,650	
Acetylcysteine (= 0,52 g L-cysteine)	0,70	(0.52)	1,050	(0.78)

L-fenylanaline	0,88	1,320
L-treonine	4,40	6,600
L-tryptophane	0,70	1,050
L-valine	10,08	15,120
L-arginine	10,72	16,080
L-histidine	2,80	4,200
Aminoacetic acid (glycine)	5,82	8,730
L-alanine	4,64	6,960
L-proline	5,73	8,595
L-serine	2,24	3,360
Acetic acid	4,42	
Total amino acids	**83,01 g/L**	**124,52 grams**
Total nitrogen	12,90 g/L	
Osmolarity	**770 mosm/L**	**770 mosm/L**

C. L-Lysine (total 500 mL) per unit

- L-lysine HCl 5% 500 mL (=25 grams of L-lysine)
- HCl 25% is added to achieve pH 7.4

The osmolarity of this solution is ca. 400 mosmol/L

For 50 grams of L-lysine 2 units (total 1000 mL) are used; for 75 grams of L-lysine 3 units (1500 mL). Saline (NaCl 0.9%) or a mixture of glucose and saline (NaCl 0.45% + glucose 2.5%), can be added to increase the infusion volume.

All these infusion fluids are given over a period of 4 hours, with a maximum of 2.03 L per 4 hours. The rate of infusion can be constant over 4 hours, but initial high rates of infusion followed by lower rates of infusion are employed also. These infusion fluids can be given for periods up to 12 hours, with maximal average infusion rates of 2.03 L per 4 hours.

EXAMPLE 1

Effect of intravenous Lysine/Arginine infusion on tissue uptake

A 1000 mL infusion containing 25 g L-lysine and 25 g L-arginine (**Lys/Arg**; see MATERIALS, paragraph A. for

exact formulation) was administered intravenously to patients during 4 hours, starting 30 minutes prior to administration of the radioligand. One radioligand was [^{111}In-DTPA-D-Phe^{1}]octreotide (^{111}In-pentetreotide, OctreoScan®, Mallinckrodt Medical, Petten, The Netherlands) in a diagnostic amount of 220 MBq (9 patients). Each patient was also investigated on a separate occasion with 220 MBq ^{111}In-pentetreotide, but without any infusion. The other radioligand was [^{177}Lu-DOTA,Tyr^{3}]octreotate in a therapeutic amount of 1850 MBq (5 patients). Each patient was also investigated on a separate occasion with 1850 MBq [^{177}Lu-DOTA,Tyr^{3}]-octreotate, but without any infusion. The control experiment (5 patients) consisted of infusion of 1000 mL neutral infusion fluid without the amino acids (NaCl 0.45% plus Glucose 2.5%)over 4 hours, starting 30 min. prior to the injection of 220 MBq ^{111}In-pentetreotide.

24 Hours post infusion the uptake of the radioligand in the kidneys, spleen and liver was measured using planar scintigraphy and dosimetry, and for each patient the ratio between uptake in these organs during infusion with **Lys/Arg** and without **Lys/Arg** was calculated (Figures 1, 2 and 3).

In the 9 patients who received a diagnostic dose of 220 MBq of ^{111}In-pentetreotide, during **Lys/Arg** infusion the mean uptake of the radioligand in the kidneys was reduced to 68% (left) and 52% (right) of their own control without **Lys/Arg** (Figure 1).

In the 5 patients who received a therapeutic dose of 1850 MBq [^{177}Lu-DOTA,Tyr^{3}]octreotate, during **Lys/Arg** infusion the mean uptake of the radioligand in the kidneys was reduced to 63% (left) and 61% (right) of their own control without **Lys/Arg** (Figure 2).

The control experiment showed no significant differences in renal uptake of ^{111}In-pentetreotide whether 1000 mL of (neutral) infusion fluid was administered or not, thus ruling out the infusion volume itself as a contributing factor to reduce renal uptake of ^{111}In-

pentetreotide (Figure 3).

From these combined results it follows that there is a 40% decrease of ^{111}In-pentetreotide or [^{177}Lu-DOTA,Tyr^3]octreotate uptake in the kidneys during **Lys/Arg** infusion as compared to the control.

EXAMPLE 2

Effect of Lys/Arg infusion on serum potassium levels

In an experiment of the invention 11 patients received an infusion over 4 hours of a solution containing 25 g L-lysine and 25 g L-arginine in 1000 mL (**Lys/Arg**; see MATERIALS, paragraph A. for exact formulation). The potassium level of these patients was measured in serum at t=0 hours and after 0.5, 1, 2, 4 and 5 hours. The results are shown in table 1 and figure 4.

Table 1

Potassium level in serum during infusion of 1000 mL Lys/Arg over 4 hours, starting 30 min. prior to the administration of ^{111}In-pentetreotide in a diagnostic amount of 220 MBq.

patient no.	0	0.5	1	2	4	5	max. difference
1	4.6	4.6	4.9	5.4	5.5	5.4	0.9
2	4.2	4.1	4.6		4.8		0.7
3	4.3	4.5	4.7	4.9	5.4	4.8	1.1
4	4.5	4.7	5.3	6.0	5.7		1.5
5	4.5	4.5		5.0	5.3		0.8
6	4.1	4.2		5.1	5.2	5.3	1.1
7	4.4	4.1		4.5	5.0		0.6
8	3.7	3.3		3.9	4.5	4.4	0.8
9	3.0	3.0		3.6	4.0		1
10	4.3	4.3		4.8	5.5		1.2

11	4.5	n.d.	4.4	4.9	4.8		0.4
Average	4.2	4.1	4.8	4.8	5.1		0.9

As a control 6 patients received 75 g L-lysine in 1500 mL during 4 hours (see MATERIALS, paragraph C. for exact formulation). Their maximum serum potassium levels are given in Table 2.

Table 2

Maximum potassium level in serum during infusion of 75 g L-lysine in 1500 mL over 4 hours, starting 30 min. prior to the administration of ^{111}In-pentetreotide in a diagnostic amount of 220 MBq (patients 12, 13, 14, 15), or in a therapeutic amount of 7 GBq (patients 16, 17).

patient	maximum potassium (K) level
12	5.2
13	**6.8**
14	**6.7**
15	5.4
16	5.0
17	**6.3**

Patient no. 17 showed transient muscle weakness, the other patients had no symptoms related to the infusion.

EXAMPLE 3

Effect of different amino acid preparations on [^{111}In-DTPA]octreotide uptake in the kidney

At least 5 patients received one of the following amino acid preparations:

1. AA (2030 mL cocktail of various amino acids; see MATERIALS, paragraph B, for the source and details)

2. 25 g L-lysine in 500 mL (see MATERIALS, paragraph C, for exact formulation)
3. 50 g lysine in 2000 mL (see MATERIALS, paragraph C, for exact formulation)
4. 75 g lysine in 1500 mL (see MATERIALS, paragraph C, for exact formulation)
5. 25 g L-lysine and 25 g L-arginine in 1000 mL (invention), (**Lys/Arg**; see MATERIALS, paragraph A. for exact formulation).

The preparations were given intravenously over 4 hours starting 30 minutes before treatment with the radioligand started. The radioligand was ^{111}In-pentetreotide, either in a diagnostic amount of 220 MBq, or in a therapeutic amount, 7 - 11 GBq. Each patient was his or her own control. The control consisted of treatment with the radioligand but without an amino acid preparation.

At 24 and 48 hours post infusion the ratio between tissue uptake in the left kidney in patients receiving an amino acid composition and the controls was determined by planar scintigraphy and dosimetry.

Figure 4 gives the results of this study, which also includes the data obtained in patients described in examples 1 and 2. Although 75 g L-lysine leads to the highest uptake reduction, it was found that it resulted in severe hyperkalemia (Table 2). No hyperkalemia was found in the second best amino acid composition comprising 25 g L-lysine plus 25 g L-arginine (Table 1). Moreover, it was found that more patients vomited that received the AA compositions than patients receiving L-lysine or Lys/Arg(see also EXAMPLES 4, 5, 6).

EXAMPLE 4

Effect of prior art amino acid composition on vomiting

26 patients received 1 to 5 therapeutic doses of 1-10 GBq ^{90}Y-DOTA,Tyr^3-octreotide, with concomitant infusion of a 2030 mL cocktail of various amino acids in

4 hours, starting 30 min. before the administration of the radiopharmaceutical (see MATERIALS, paragraph B. for exact details). In 11 of these 26 patients (42%), [being 20 of 84 treatments (24%)] one or more episodes of vomiting occurred, up to 30 episodes of severe vomiting per treatment.

In one of these 11 patients the vomiting was so severe during the 2 treatments with the above described regimen, that it was decided to use an infusion with 50 g of L-lysine instead of the infusion with the cocktail of various amino acids concomitant with his 3rd and 4th therapy with ^{90}Y-DOTA,Tyr^3-octreotide. Only one episode of vomiting occurred after his 3rd treatment and no vomiting at all after his 4th treatment.

EXAMPLE 5

Effect of lysine on vomiting

8 patients received multiple therapeutic doses of 7-11 GBq ^{111}In-pentetreotide. All received once a concomitant infusion of a 2030 mL cocktail of various amino acids in 4 hours, starting 30 min. before the administration of the radiopharmaceutical (see MATERIALS, paragraph B. for exact details). In 4 of these 8 patients (50%) vomiting occurred.

In these same 8 patients only 3 episodes (9%) of vomiting occurred during 22 treatments with 7-11 GBq ^{111}In-pentetreotide while they received 25 or 50 grams of L-lysine in 500 to 2000 mL (see MATERIALS, paragraph C. for exact details) over 4 hours, starting 30 min. before administration of the radiopharmaceutical, as concomitant infusions.

In these same 8 patients only 3 episodes (6%) of vomiting occurred during 52 treatments while they received no concomitant infusion at all.

EXAMPLE 6

Effect of **Lys/Arg** on vomiting

In an experiment of the invention 11 patients received an infusion over 4 hours of a solution containing 25 g L-lysine and 25 g L-arginine in 1000 mL (**Lys/Arg**; see MATERIALS, paragraph A. for exact formulation). Thirty min. after the start of the infusion they received a diagnostic dose of 220 MBq ^{111}In-pentetreotide. Ten patients had no symptoms during the infusion, in particular no vomiting. One patient had subfebrile temperature, malaise and nausea already before the start of the infusion, presumably caused by tumor necrosis. During the **Lys/Arg** infusion she vomited twice. This patient has tolerated the **Lys/Arg** infusion without any problems on all 4 later occasions, while receiving a therapeutic dose of 10-11 GBq ^{111}In-pentetreotide.

Five patients received the **Lys/Arg** infusion in the same manner as described above, but they received a therapeutic dose of 1850 MBq [^{177}Lu-DOTA,Tyr^3]octreotate, 30 min. after the start of the **Lys/Arg** infusion. None of these 5 patients had any symptoms at all, in particular no vomiting.

Until now the **Lys/Arg** infusion, 1000 mL in 4 hours concomitant with therapeutic doses of radioactive labelled peptides, has been administered to more than 30 patients, in total more than 80 occasions. Vomiting occurs in less than 5% of the occasions, and if it occurs it is most probably due to other causes.

From these studies described in EXAMPLES 4, 5 and 6 it was concluded that the infusion of 2030 mL containing a cocktail of various amino acids causes frequent vomiting, which is unacceptable for routine clinical circumstances. On the other hand, vomiting is seldomly observed either with L-lysine infusions or with **Lys/Arg** infusion.

CLAIMS

1. Use of the combination of:

- a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof, and

- a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof,

for the preparation of a composition for inhibiting renal uptake of substances, in particular proteins or peptides, that may be damaging to the kidneys, and that are used for therapeutical or diagnostic purposes.

2. Use as claimed in claim 1, wherein the positively charged second molecule is a positively charged amino acid, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

3. Use as claimed in claim 2, wherein the positively charged amino acid is selected from the group consisting of arginine, ornithine and citrulline, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

4. Use as claimed in claims 1-3, wherein the first compound is lysine selected from D-lysine, L-lysine or poly-lysine.

5. Use as claimed in claims 1-4, wherein the first compound is lysine and the second compound is arginine.

6. Use as claimed in claims 1-5, wherein the amount of the first compound is 10-45 grams, preferably 15-35 grams, more preferably 20-30 grams, most preferably about 25 grams per treatment.

7. Use as claimed in claims 1-6, wherein the amount of the second compound is 15-45 grams, preferably 15-35 grams, more preferably 20-30 grams, most preferably about 25 grams per treatment.

8. Use as claimed in claims 1-7, wherein the first compound is lysine in an amount of about 25 grams and the second compound is arginine in an amount of about 25 grams per treatment.

9. Use as claimed in claims 1-8, wherein the two compounds are administered in about 1 L infusion fluid over a period of about 4 hours.

10. Use as claimed in claims 1-9, wherein the substances that may be damaging to the kidneys, and of which the renal tubular uptake is to be inhibited are proteins, peptides or monoclonal antibodies, in particular proteins, peptides or monoclonal antibodies that are inherently toxic, that are coupled to a radionuclide, a cytostatic agent, a toxic agent, a metal, or a combination thereof, or cytostatic agents and nephrotoxic antibiotics per se.

11. Therapeutical composition for the inhibition of the renal uptake of substances, in particular proteins or peptides, that may be damaging to the kidneys and that are used for therapeutical or diagnostic purposes, which composition comprises one or more pharmaceutically acceptable excipients, carriers or diluents and a combination of

- a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof, and

- a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

12. Therapeutical composition as claimed in claim 11, wherein the positively charged second molecule is a positively charged amino acid, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

13. Therapeutical composition as claimed in claim 12, wherein the positively charged amino acid is selected from the group consisting of arginine, ornithine

and citrulline, or pharmaceutically acceptable salts or carboxyl derivatives thereof.

14. Therapeutical composition as claimed in claims 11-13, wherein the first compound is lysine selected from D-lysine, L-lysine or poly-lysine.

15. Therapeutical composition as claimed in claims 11-14, wherein the first compound is lysine and the second compound is arginine.

16. Therapeutical composition as claimed in claims 11-15, wherein the amount of the first compound is 10-45 grams, preferably 15-35 grams, more preferably 20-30 grams, most preferably about 25 grams per treatment.

17. Therapeutical composition as claimed in claims 11-16, wherein the amount of the second compound is 15-45 grams, preferably 15-35 grams, more preferably 20-30 grams, most preferably about 25 grams per treatment.

18. Therapeutical composition as claimed in claims 11-17, wherein the first compound is lysine in an amount of about 25 grams and the second compound is arginine in an amount of about 25 grams per treatment.

19. Therapeutical composition as claimed in claims 11-18, wherein the two compounds are present in about 1 L infusion fluid.

20. Method for inhibiting the renal uptake of proteins or peptides, that are used for therapeutical or diagnostic purposes, in a subject, which method consists of the administration of a therapeutical composition as claimed in claims 11-19.

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(54) Title: INHIBITION OF RENAL UPTAKE OF RADIOMOLECULES WITH A COMBINATION OF LYSINE AND ARGININE

(57) Abstract: The invention relates to the use of the combination of a first compound which is lysine, or an amino acid or other proteinaceous moiety having a free amino group with a pKa substantially similar or equal to that of lysine, or pharmaceutically acceptable salts or carboxyl derivatives thereof, and a second compound, which is a positively charged compound, or pharmaceutically acceptable salts or carboxyl derivatives thereof, for the preparation of a composition for inhibiting renal uptake of substances, in particular proteins or peptides, that may be damaging to the kidneys, and that are used for therapeutical or diagnostic purposes. The combination consists advantageously of lysine and arginine.

Figure 1

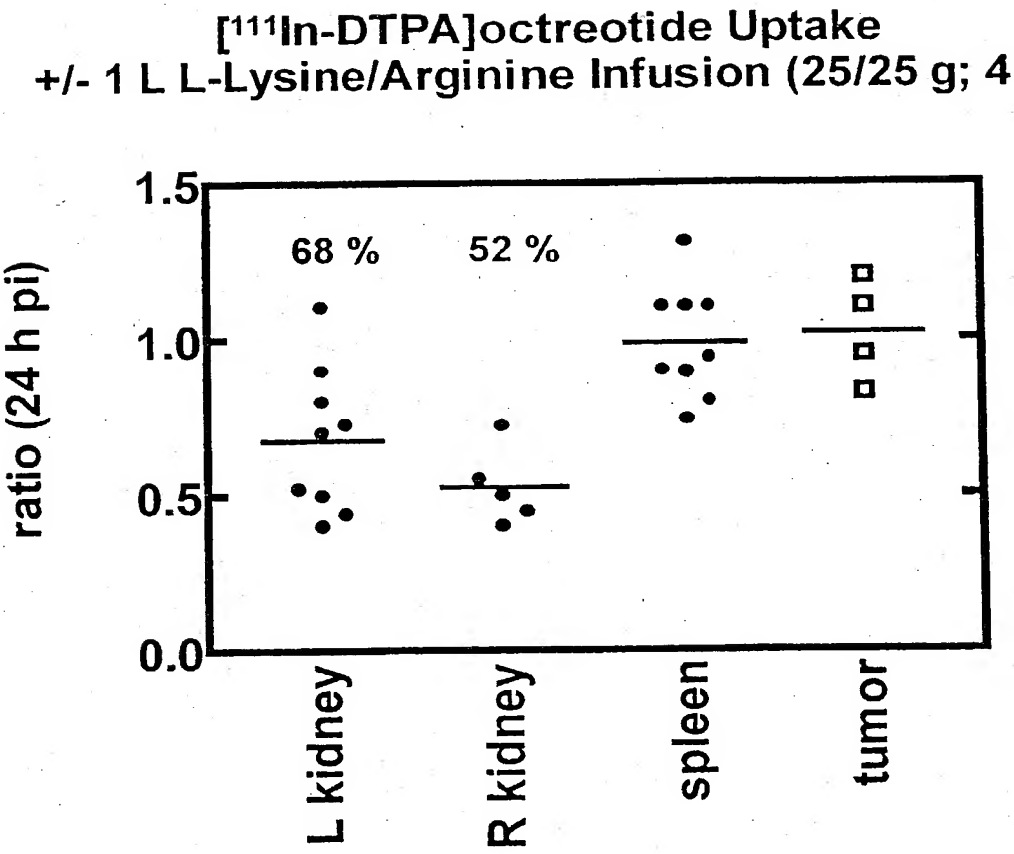

[111In-DTPA]octreotide Uptake
+/- 1 L L-Lysine/Arginine Infusion (25/25 g; 4 h)
ratio (24 h pi)
1.5
1.0
0.5
0.0
68 %
52 %
L kidney
R kidney
spleen
tumor

Figure 2

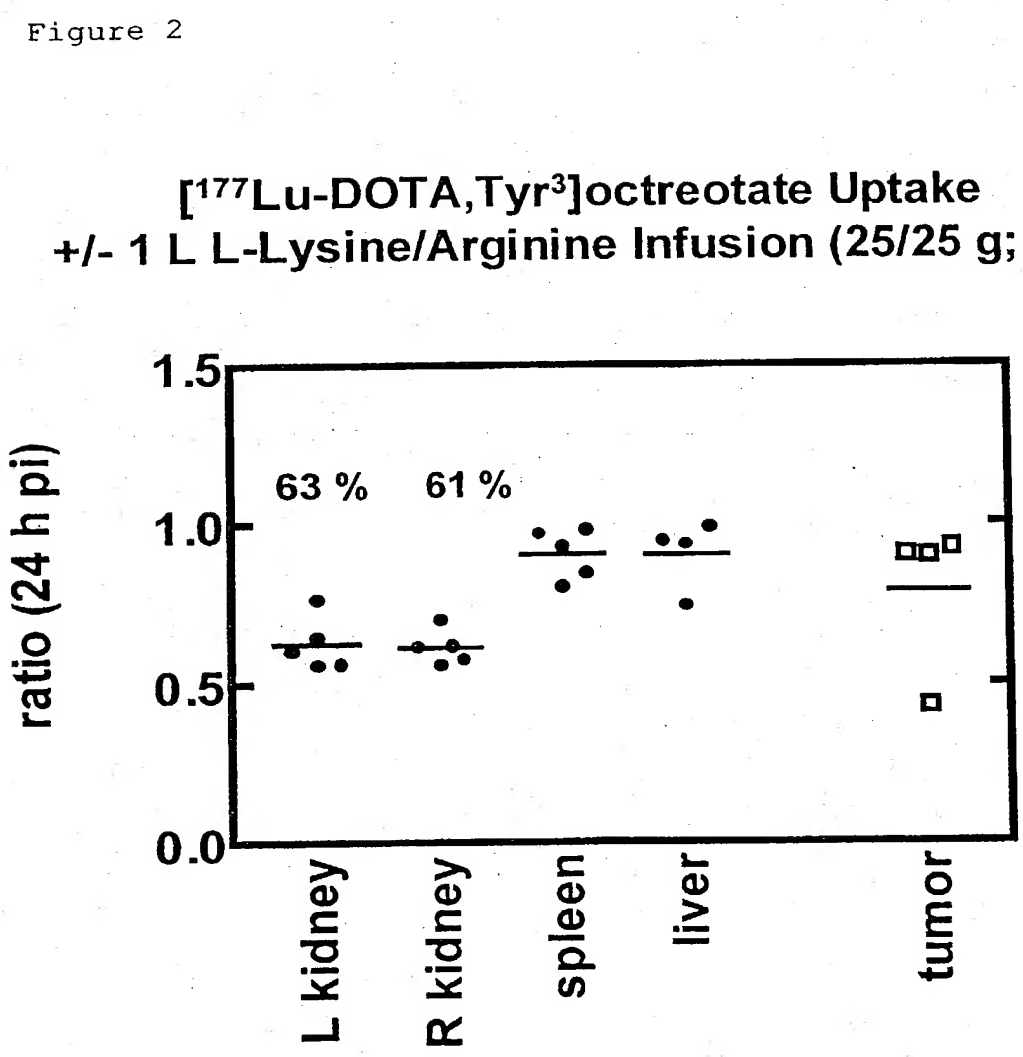

[177Lu-DOTA,Tyr3]octreotate Uptake
+/- 1 L L-Lysine/Arginine Infusion (25/25 g; 4 h)
ratio (24 h pi)
1.5
1.0
0.5
0.0
63 %
61 %
L kidney
R kidney
spleen
liver
tumor

Figure 3

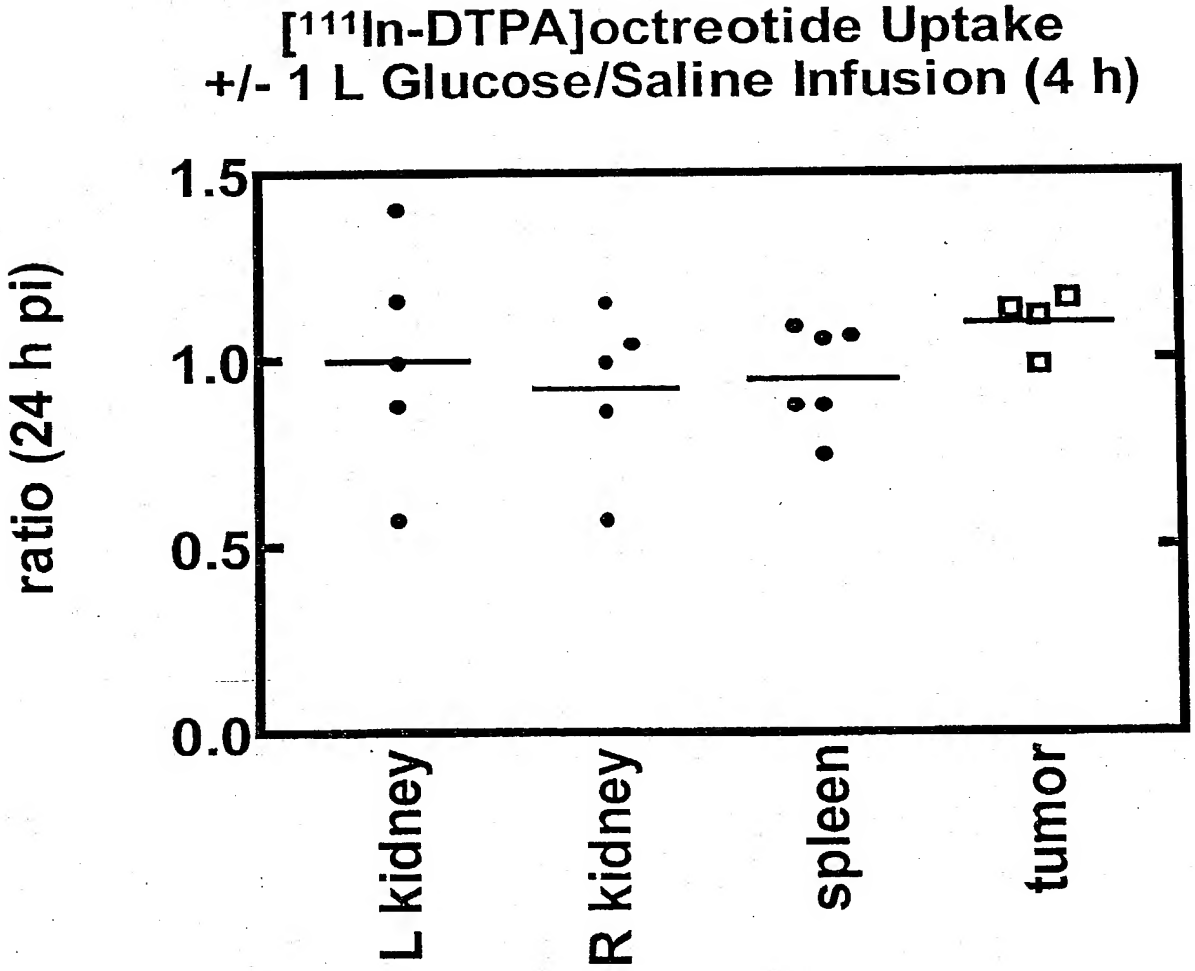
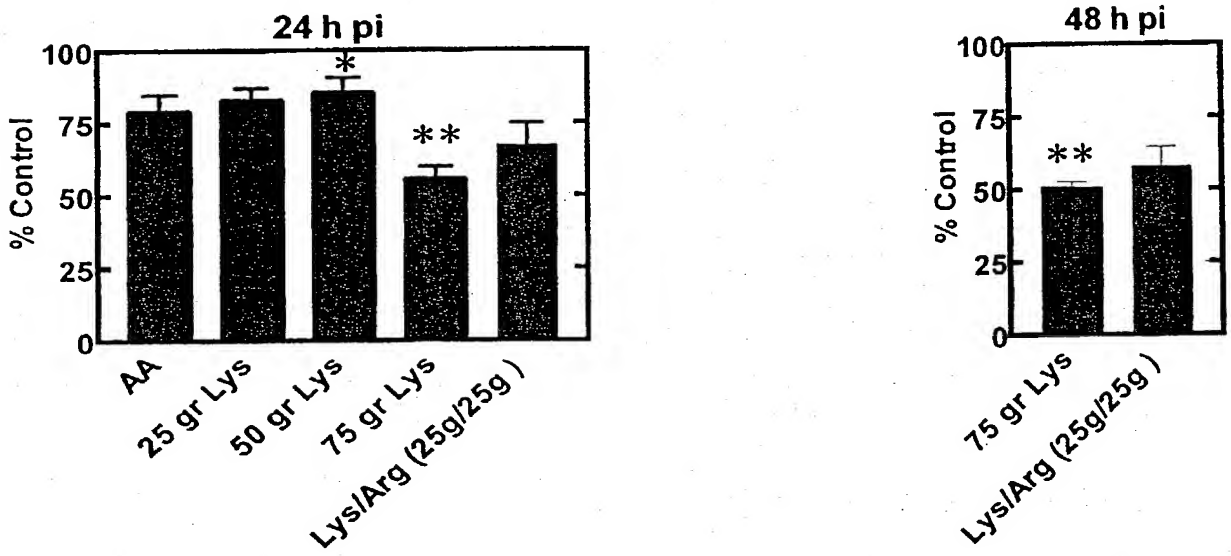

[111In-DTPA]octreotide Uptake
+/- 1 L Glucose/Saline Infusion (4 h)
ratio (24 h pi)
1.5
1.0
0.5
0.0
L kidney
R kidney
spleen
tumor

Figure 4

[^{111}In-DTPA]octreotide Uptake in Left Kidney Effect of 0.5 + 3.5 h AminoAcid Infusion



Versus Lys/Arg (25g/25g): * $p < 0.04$, ** $p > 0.10$

M $\pm$ SEM; N $\geq$ 5

#4

Declaration and Power of Attorney for Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled
" Inhibition Of Renal Uptake Of Molecules That Are Potentially Damaging For The Kidney"

The specification of which

(check one)

0 is attached hereto.

X was filed on January 16, 2002

as Application Serial No. 10/031,509

and was amended on January 16, 2002 (if applicable)

0 was filed as PCT international application

No. PCT/EP00/06917 on 17 July 2000

and was amended under PCT Article 19 on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
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_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	0 Yes	0 No
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	0 Yes	0 No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list name and registration number)

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